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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,967	ALL-ERICSSON ET AL.	
	Examiner	Art Unit	
	LESLIE A. ROYDS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2 and 4-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2 and 4-7 are presented for examination.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 27, 2009 has been received and entered into the present application. Accordingly, prosecution has been reopened.

Claims 1-2 and 4-7 are pending. Claims 1 and 6 are amended.

Applicant's arguments, filed March 27, 2009, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Objection to the Oath/Declaration (New Grounds of Objection)

The oath or declaration filed September 13, 2005 is defective because the declaration contains handwritten changes to each inventor's residence that have not been initialed or dated by the individual(s) who executed the declaration. A new oath or declaration in compliance with 37 C.F.R. 1.67(a) identifying this application by serial number and filing date is required. Please reference MPEP §§602.01 and 602.02.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement, New Matter (New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 4-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In particular, the specification and claims as originally filed fail to provide adequate written description for the newly added limitation directed to a "therapeutically effective" dose of 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide or a pharmaceutically acceptable salt thereof (claim 1).

MPEP §2163 states, "The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test of sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983))…Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in

possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)."

Applicant provides relevant disclosure at p.3, para.3, of the instant specification, which states: "The invention relates to a method of treating a warm-blooded animal having uveal melanoma comprising administering to said animal in need for such a treatment Compound I or a pharmaceutically acceptable salt thereof, in a quantity which is therapeutically effective against uveal melanoma."

The disclosure of the use of, specifically, an amount of Compound I or a pharmaceutically acceptable salt thereof (which, for the record, Compound I is equivalent to the active agent 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide as evidenced by Applicant's disclosure at p.1 of the instant specification) that is therapeutically effective against uveal melanoma fails to provide adequate written support to now broaden the claims to read upon simply an amount that is *therapeutically effective* wherein the desired therapeutic effect is not specified. This is a concept that is not adequately supported by the written description of the invention as provided in the specification and claims as originally filed because the specific disclosure of an amount of the compound 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide or a pharmaceutically acceptable salt thereof that is therapeutically effective against uveal melanoma does not provide adequate support to then broaden the claims to read upon the use of an amount of the same that is simply *therapeutically effective*. This newly amended limitation represents a broadening of the subject matter both claimed and disclosed in the specification and claims as originally filed that is not adequately supported, either explicitly or implicitly, by the original disclosure and clearly circumscribes a concept that was not in Applicant's possession at the time of the invention.

Note, further, that the therapeutic effectiveness of the dose as now claimed is not explicitly tied to the preamble objective of treating uveal melanoma. In fact, the claim as presently written do not specify the particular therapeutic objective of the claimed method in the preamble of the claim because instant

claim 1 is directed to a "method of treating a mammal suffering from uveal melanoma", but does not expressly state that the purpose of the method is to actually *treat the uveal melanoma*. Accordingly, the claims as presently written do not explicitly or implicitly specify the function of the therapeutically effective quantity as being effective against uveal melanoma, as disclosed in the specification and claims as originally filed.

As stated in MPEP §2163, "The subject matter of the claim need not be described literally (i.e., using the same terms of *in haec verba*) in order for the disclosure to satisfy the description requirement." However, considering the teachings provided in the specification as originally filed, Applicant has failed to provide the necessary teachings, by describing the claimed invention in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the concept of a "therapeutically effective" dose of 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide or a pharmaceutically acceptable salt thereof (claim 1).

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 and 4-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 1 is directed to a method of treating a mammal suffering from uveal melanoma comprising administering to said mammal in need of such treatment a therapeutically effective dose of 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide

or a pharmaceutically acceptable salt thereof.

In particular, the claims fail to clearly set forth what, in fact, in being treated by the instantly claimed method. Specifically, the claims as presently written do not specify the particular therapeutic objective of the claimed method in the preamble of the claim because instant claim 1 is directed to a "method of treating a mammal suffering from uveal melanoma", but does not expressly state that exact purpose of the method, e.g., to actually treat the uveal melanoma or some other condition in a mammal suffering from uveal melanoma. Accordingly, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection. Clarification is requested.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

For the purposes of examination, the claims will be interpreted to read upon a method for treating uveal melanoma in a mammal suffering from uveal melanoma comprising administering the instantly claimed compound or a pharmaceutically acceptable salt thereof.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of

each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 and 4-7 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman et al. (WO 99/03854; 1999) in light of Mouriaux et al. ("Implication of Stem Cell Factor in the Proliferation of Choroidal Melanocytes", *Exp. Eye Res.*, 2001; 73:151-157), cited as evidence, in view of Ijland et al. ("Expression of Angiogenic and Immunosuppressive Factors by Uveal Melanoma Cell Lines", *Melanoma Research*, 1999; 9:445-450), each already of record, for the reasons of record set forth at p.3-9 of the previous Office Action dated March 26, 2008, of which said reasons are herein incorporated by reference.

Newly amended claim 1 remains properly included in the present rejection because Zimmerman et al. teaches the beta-crystal form of the methanesulfonic acid addition salt of 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide as useful for the treatment of warm-blooded animals suffering from tumor diseases, wherein a quantity of the beta-crystal form of the methanesulfonic acid addition salt of the compound effective against the disease concerned is administered to the warm-blooded animal in need of such treatment (p.17, para.1). Zimmerman et al. further discloses that an exemplary study of an oral dose of 50 mg/kg of the disclosed compound once daily was effective to inhibit the angiogenic effect of VEGF (p.16, para.2), i.e., a "therapeutically effective dose" as now claimed in instant claim 1.

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that Mouriaux et al. teaches that the addition of SCF (c-kit ligand) to the medium did not change the melanocyte morphologies and did not induce proliferation in the absence of two other factors such that SCF was only determined to be mitogenic only

in the presence of other factors. Applicant alleges that the disclosure of Mouriaux et al. does not lead one of skill in the art to expect that a c-kit inhibitor (i.e., imatinib) would be useful for uveal melanoma. Applicant argues that the combination of Zimmerman et al. and Ijland et al. provides for no more than a hypothesis that imatinib may be useful for uveal melanoma and that the skilled artisan would not have had a reasonable expectation of success without performing experiments to such an effect. Applicant further states that the proffered data is evidence of unexpected results, emphasizing that "it is reasonable to rely on data from the mesylate salt for the patentability of the full range of pharmaceutically acceptable salts" (p.4, Remarks) Applicant additionally emphasizes that "there is a clear effect in all cell lines at the high doses after 48 hours" and asserts that, in each of the cell lines tested, at least 75% of the cells die after 48 hours at the 5 and 10 micromolar concentrations and a clear dose response over all concentrations is seen in 2 cell lines.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Firstly, Applicant's traversal with regard to the application of Mouriaux et al. is unclear. Mouriaux et al. was cited solely for its teaching that activation of c-kit by its ligand was known to contribute to the proliferation of choroidal melanocytes, which are the cells involved in the pathogenesis of malignant melanoma of the eye and, therefore, one of skill in the art at the time of the invention would have reasonably expected that the uveal melanoma cells would have expressed c-kit.

The obviousness, however, of using the 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide for the treatment of uveal melanoma was not based upon the activity of this compound as a c-kit inhibitor. Rather, the asserted obviousness of using this active compound for treating uveal melanoma was based upon the fact that (1) Zimmerman clearly discloses the active compound as an effective inhibitor of the angiogenic effect of VEGF and (2) Ijland et al. clearly discloses that six different human primary uveal melanoma cell lines (92-1, Mel-202, OCM-1, OCM-3, OCM-8 and EOM-3) each demonstrated significant VEGF secretion, which was indicative of

angiogenic potency and vessel proliferation for neovascularization and, thus, the use of a compound that clearly inhibits angiogenesis associated with VEGF for treating a disease that clearly exhibits angiogenesis as a result of significant VEGF secretion would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention. Such a person would have had a clearly reasonable expectation of success in treating uveal melanoma with such a compound because the inhibition of angiogenesis caused by VEGF expression would have inhibited the neovascularization necessary for tumor growth.

In that line, Applicant opines that there is no reasonable expectation of success without performing experiments to such effect. However, this is unpersuasive because Applicant is applying a standard of absolute predictability in order to find obviousness, which is not required. Rather, to find obviousness, only a reasonable expectation of success is required, which is provided *supra* and in the rationale provided in each of the previous Office Actions (to which Applicant's attention is directed). Please see MPEP §2143.02 and *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976).

Secondly, Applicant's insistence that it is reasonable to rely upon data from the mesylate salt to predict the activity of other pharmaceutically acceptable salts is unpersuasive. Applicant advances no other specific reasons or evidence, aside from Counsel's own speculation, in support of this position. This assertion by Counsel is an unsupported allegation that the activity seen with the mesylate salt is predictive of the same activity of any or all other pharmaceutically acceptable salts. Statements of this nature are clearly unpersuasive in accordance with the guidance provided at MPEP §2145, which states, "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)".

Thirdly, Applicant again references the data provided in the instant specification as evidence of unexpected activity. However, Applicant's allegations that the present invention is non-obvious over the prior art because the use of the methanesulfonate salt of 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-

3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide demonstrated an unexpected anti-proliferative effect in four uveal melanoma cell lines (OCM-1, OCM-3, UM 92-1 and mel 202) as reflected in the data presented in the Table at p.5 of the instant specification is again, as before, unpersuasive. While such results have been carefully and closely considered, it remains that (1) the compound used in the example was the methanesulfonate salt of 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide, whereas the presently claimed subject matter is directed to the use of 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide or any pharmaceutically acceptable salt thereof, and (2) several of the concentrations of methanesulfonate salt of 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide, in fact, demonstrated an increase in cell proliferation in certain uveal melanoma cell lines and/or failed to demonstrate an unexpectedly potent anti-proliferative effect in the cell lines studied, whereas the presently claimed subject matter is directed to the use of any therapeutically effective dose of 4-(4-methyl piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2-ylamino)phenyl]-benzamide or a pharmaceutically acceptable salt thereof (but, as noted *supra*, not necessarily a dose that is *therapeutically effective for the treatment of uveal melanoma*). Furthermore, as evidenced by the data in the Table at p.5 of the specification, it appears that the dose and the amount of time that said dose of the compound is allowed to incubate with the uveal melanoma cells is clearly pertinent to achieving Applicant's allegedly unexpected anti-proliferative effect. Applicant fails to address these deficiencies in the remarks provided in the instant submission to clarify how this data is commensurate in scope with the claimed subject matter and, thus, is representative of the same unexpected effects over the full scope of the claims, since the claims are not limited to those embodiments that have been shown to be, in fact, unexpected. For these reasons, Applicant's remarks regarding the non-obviousness of the instant claims over the cited prior art are unpersuasive.

Moreover, Applicant's reliance upon the "extensive clinical experience with imatinib since its approval in 2001 as a targeted cancer therapy" as providing additional support to the assertion that the unexpected effects would be observed over the full range of the present claims is also unpersuasive because Applicant has failed to point to, specifically, what evidence he particularly believes lends support to this assertion that the limited unexpected embodiments demonstrated in the instant specification are suggestive of the same effects over the full scope of the present claims.

In view of the foregoing, the totality of rebuttal evidence of nonobviousness fails to outweigh the evidence in support of the instant conclusion of *prima facie* obviousness when all of the evidence and remarks are considered. Accordingly the rejection is properly maintained.

For these reasons *supra*, and those previously made of record at p.3-9 of the Office Action dated March 26, 2008, rejection of claims 1-2 and 4-7 is proper.

Conclusion

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Please reference U.S. Patent Application Publication No. 2004/0127470 to Masferrer et al. ("Methods and Compositions for the Prevention or Treatment of Neoplasia Comprising a COX-2 Inhibitor in Combination with an Epidermal Growth Factor Receptor Antagonist").

Rejection of claims 1-2 and 4-7 is proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LESLIE A. ROYDS whose telephone number is (571)272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

April 14, 2009